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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,420	01/26/2001	Sui Xiong Cai	1735.0440001/RWE/BEC	4240

26111 7590 12/19/2003

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	20

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,420	CAI ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-43,46,47,51,52,58-61,71,76 and 79-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *58-61,71 and 79* is/are allowed.

6)☒ Claim(s) *33-43,46,47,51,52,76,82 and 83* is/are rejected.

7)☒ Claim(s) *80 and 81* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 10/10/03. Applicant has amended claims 33, 39, 41, 59, and 79. Claims 80-83 are new. There are twenty-six claims pending and twenty-six under consideration. Claims 58-61 and 79 are compound claims. Claim 71 is a composition claim. Claims 33-43, 46, 47, 51, 52, 76, and 80-83 are use claims. This is the fourth action on the merits. The application concerns some nicotinamide compounds, compositions, and uses thereof.

Response to Amendments and arguments

2. Deletion of the relevant compounds from claims 59 and 61 overcomes the indefiniteness rejections made in points #3 and #4 of the previous office action. Applicants' argument that one of radical R_1 and R_5 are required to be NO_2, CN, or alkyl is persuasive. This proviso was present when the Application was filed. None of the compounds taught by Mantlo ('884), Von der Saal (DE 3,804,346 A), Setliff (Proceedings of the Arkansas Academy of Science, 1995), Austel ('348), Persons (Proceedings of the Arkansas Academy of Science.), and Setliff (Proceedings of the Arkansas Academy of Science, 1995) have this required feature. Thus the anticipation rejections made in points #6-#11 are withdrawn. The Examiner regrets the error. Full text copies of Setliff (Proceedings of the Arkansas Academy of Science, 1995), Persons (Proceedings of the Arkansas

Academy of Science.), and Setliff (Proceedings of the Arkansas Academy of Science, 1995) are provided to complete the record.

Applicants deletion of R_1 = hydrogen from the Markush lists overcomes the anticipation rejection over Shudo (JP 6/263,702 A2), Klebanov (Fiziologicheski Aktivnye Veshchestv), Bukhtiarova (Khimiko-Farmatsevticheskii Zhurnal), and Miryan (Khimiko-Farmatsevticheskii Zhurnal). All compounds taught in these references have a hydrogen atom at position R_1. Thus the anticipation rejections made in points #12-#15 are overcome. Translations of Shudo (JP 6/263,702 A2), Kubota (WO 99/19303 A1) and Bukhtiarova (Khimiko-Farmatsevticheskii Zhurnal) as well as complete copies of Klebanov (Fiziologicheski Aktivnye Veshchestv), Bukhtiarova (Khimiko-Farmatsevticheskii Zhurnal), and Miryan (Khimiko-Farmatsevticheskii Zhurnal) are included to complete the record.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-43, 46, 47, 51, 52, and 76 remain rejected and claims 82 and 83 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the five named leukemia diseases of claim 82, breast, and cervical carcinomas, does not reasonably provide enablement for

treating all other claimed cancers or inflammatory diseases. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Determining if any particular claimed compound would treat any particular cancers or inflammatory disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different cancers or inflammatory diseases, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating cancers or inflammatory diseases is found in the passage spanning line 10, page 23 to line 2, page 24, which merely states Applicants' intention to do so.

Applicants describe formulations in the passage spanning line 24, page 30 to line 31, page 32. There is no working example of any formulation, which would be required to practice Applicants invention. Doses required to practice their invention are described in lines 3-17, page 29. A 20,000-fold range of doses is recommended. Since no caspase activator has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is a *in vitro* assay described in the passage spanning line 11, page 55 to line 15, page 56 with data on thirty compounds. This assay involved activation of enzymes in breast cancer cells but it is unclear if this assay is correlated to cancers generally. There are three additional *in vitro* assays in pages 58-61. These assays employ Jurkat, breast cancer, and HeLa cells respectively. There is data on two of the compounds described above. HeLa cells are described in Stedman's Medical Dictionary as a cervical carcinoma cell line.

c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in caspase related diseases is provided by Talanian (Ann. Reports. Med. Chem.). He states that in second complete paragraph page 278 and second paragraph page 279 capase-1 (ICE) is a validated target and that inhibitors of this enzyme might be useful in

treating the inflammatory disease sepsis. Applicants' compounds are activators, have the opposite effect of inhibitors, and may well make the inflammatory disease sepsis worse. Miller (Ann. Reports Med. Chem.) states in the forth paragraph, page 261 that it is unknown if blockage is therapeutically meaningful. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the millions of compounds of claim 33 as well as the dozens of listed diseases. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.

Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants point out that Jurkat cells were used in the testing described in the specification. The On-Line Medical Dictionary defines Jurkat cells as "a cell line derived from human T-cell leukaemia". Thus, the five leukemia diseases named in new claim 82 are also enabled.

Applicants discuss five of the eight enablement factors, presumably agreeing with points d), f), and g). Applicants discuss point c) but can point to no working example of a formulation or working example of disease treatment in a living organism. Applicants agree that millions of compounds are encompassed by the claims but fail to discuss the number of fundamentally different diseases embraced by the claims. They assert that a representative number of compounds have been tested. However, no rejection was made as to compounds only the different diseases intended. They do not dispute that the scope of claims is very broad, made in point h). They only dispute the conclusion made by the Examiner that the experimentation is undue. Applicants dispute the degree of experimentation required. They agree that it is time consuming but state that it is not undue. This is a conclusion. Since no assays, correlated to the rejected diseases, are used in the specification, the experimentation will not be routine. That, coupled with the

admittedly time consuming nature of the experimentation, means that in factor a) a large degree of experimentation will be required. Do Applicants assert that it is small?

Applicants again assert discovery of suitable formulations and doses is routine but provide no evidence. Assertion is not evidence. In the previous office action in point b), the Examiner asked how a skilled physician would know what dose to use for each of these different diseases in view of the fact that no caspase activator has ever been used to treat any human disease. If Applicants cannot answer the question, how is that average physician to proceed? How is the skilled physician to know what dose to use for each of these different diseases?

Applicants dispute the state of the art reported by the Examiner in point e), yet do not supply any evidence of their own. Applicants can point to no reference showing clinical use usage of any caspase activator. The silence as to clinical usage in the references cited by the Examiner means that no such usage was known. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single

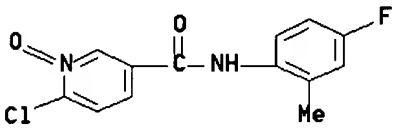
species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work."

Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics,* 211 USPQ 907, *In re Langer,* 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

Allowable Subject Matter

4. Claims 58-61, 71, and 79 are allowed. Claims 80 and 81 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any

intervening claims. The following is a statement of reasons for the indication of allowable subject matter: Applicants' compound claims 58-61, 71, and 79 are novel over Cutshall (WO 2002/053544 A1) who teaches the compound shown below. This has the required R_1 alkyl substituent but formula (III) does not permit the pyridine ring to be an N-oxide, as shown in the reference. Applicants' list of possible prodrugs does not include this possibility.



Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for after final amendments is (703) 872-9307. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Richard L. Mukund Shah
Acting SPE
Art Unit 1624

Supervisory Patent Examiner
Art Unit 1624

TCMcK